



FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2013/2014

Fátima Vanessa Santos Carvalho

Neuropsychiatric symptoms in auto-immune encephalopathies

- a clinician's guide

março, 2014

FMUP



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Mestrado Integrado em Medicina

Área: Neurociências clínicas e saúde mental

Trabalho efetuado sob a Orientação de:

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E sob a Coorientação de:

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Trabalho organizado de acordo com as normas da revista:

**International Journal of Clinical Neurosciences and Mental
Health**

março, 2014

FMUP

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Faculdade de Medicina da Universidade do Porto, 20/03/2014

Assinatura conforme cartão de identificação:

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DATA DE CONCLUSÃO

200803069

03/2014

DESIGNAÇÃO DA ÁREA DO PROJECTO

Neurociências clínicas e saúde mental

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Neuropsychiatric symptoms in autoimmune encephalopathies – a clinician's guide

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Faculdade de Medicina da Universidade do Porto, 20/03/2014

Assinatura conforme cartão de identificação:

Fátima Carvalho

Title:

Neuropsychiatric symptoms in autoimmune encephalopathies - a clinician's guide

Running head:

Neuropsychiatric symptoms in autoimmune encephalitis

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Keywords: Clinical medicine; Paraneoplastic Syndromes; Limbic encephalitis; Psychotic Disorders; Autoantibodies; Immunotherapy

Abstract word count: 253

Body text word count: 4374

6 tables and 1 figure

Abstract

Background: The spectrum of central nervous system autoimmune disorders has recently expanded with the discovery of disorders associated with antibodies directed against the neuronal membrane surface. Although many of these disorders have an underlying malignancy and present with signs of dysfunction of the limbic system (paraneoplastic limbic encephalitis, PLE), a high proportion of cases is non-paraneoplastic. They may occur with milder symptoms, and present no abnormalities in the exams usually used in the investigation of PLE. A striking number of cases may be misdiagnosed as primary psychiatric or other neurological disorders.

Objective: Review the current knowledge on this topic, and provide physicians with an updated text on the neuropsychiatric presentation, diagnostic approach and current management of autoimmune encephalopathies.

Methods: We searched Pubmed for articles in English until December 2013, using the terms: "Autoimmune limbic encephalitis"; "Limbic encephalitis"; "Psychiatry"; "Psychotic Disorders"; "Anti-N-Methyl-D-Aspartate Receptor Encephalitis"; "Gamma-aminobutyric-acid receptor"; "Leucine-rich-glioma-inactivated 1"; "Voltage-gated-potassium channel"; "α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic-acid receptor"; "Ri"; "Ma2"; and "Hu". We restricted the search to human studies, and selected articles for further analysis. The Article reference lists were also reviewed and relevant articles retrieved for consultation.

Results: 109 articles have been reviewed, and data summarized. The authors propose a diagnostic flowchart.

Conclusions: Autoimmune encephalitis is not a rare disorder, often has a psychiatric presentation, and should be considered whenever a non-psychiatric etiology is considered. Diagnosis is often challenging, but certain clinical features should rise suspicion about an underlying autoimmune or paraneoplastic disorder, thus guiding the physician to structured investigations, including tumor screening, and adequate therapeutic interventions, namely immunotherapy.

GLOSSARY

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANNA-1: anti-neuronal nuclear antibodies 1; ANNA-2: anti-neuronal nuclear antibodies 2; ANNA-3: anti-neuronal nuclear antibodies 3; Caspr2: contactin-associated-protein relates 2; CV2/CRMP5: crossveinless-2/collapsing response mediated protein 5; FDG-PET: fluorodeoxyglucose-positron emission tomography; FLAIR: fluid-attenuated inversion recovery; GABA_BR: gamma-aminobutyric acid receptor B; GAD: glutamic acid decarboxylase ; LE: limbic encephalitis; LGI-1: leucine-rich glioma inactivated 1; NMDAR: N-methyl-D-aspartate receptor; VGKC: voltage-gated potassium channel.

INTRODUCTION

The association between antibodies and encephalopathies has been known for several decades, since paraneoplastic limbic encephalitis (PLE) was first described, back in the 1960's. Since then, the clinical spectrum of central nervous system autoimmune disorders has expanded astonishingly. In the past decade, several new antibodies against proteins and receptors involved in synaptic transmission and neuronal plasticity have been discovered in patients presenting with encephalitis. When compared to PLE, they differ in their pathophysiology, cancer association, and clinical response, since not all cases are paraneoplastic, they occur frequently in young individuals and children, and can show an impressive response to immunotherapy.(1-6)

Furthermore, while PLE is uncommon, recent data suggests a much higher prevalence of non-paraneoplastic autoimmune encephalitis (AE) than previously imagined. Autoimmune etiology was reported in 7% of patients in a sample of 203 individuals with encephalitis. This percentage might even be higher since in cases associated with unknown causes, only anti-VGKC and NMDAR antibodies were searched for. (7) Also, in the last few years, several case reports describing milder or atypical presentations have been published.

These cases of encephalitis can present predominantly or solely with psychiatric symptoms, frequently mimicking schizophreniform or mood disorders. (8-30) Hence, this diagnostic entity can present as a clinical challenge to any physician, especially neurologists and psychiatrists, whom the majority of patients seek for help first. This paper aims to review the current knowledge on this topic, and to clarify physicians about the neuropsychiatric presentation of the most common autoimmune encephalopathies, their diagnostic approach and current management.

CLINICAL PRESENTATION, WITH EMPHASIS ON NEUROPSYCHIATRIC FEATURES

Antinuclear/cytoplasmatic autoimmune encephalitis

Anti-nuclear antibodies usually occur in PLE. As the name suggests, symptoms related to limbic system involvement predominate, as individuals present with the classic triad of memory impairment, temporal lobe seizures and psychiatric symptoms. It occurs predominantly in the elderly and, like most paraneoplastic syndromes, a higher incidence is noted in women. (31)

Seizures can be subtle, and even follow an unrecognized course. Cognitive impairment, such as confusion or short-term memory dysfunction, occurs within days to weeks, and progression to dementia may be noted over time. Overall, depression, psychosis, and behavioral changes are the most usual psychiatric spectrum manifestations, sometimes accompanied by delusions and hallucinations. Patients can also experience sleep disturbances and obsessive-compulsive behavior (OCB). (31, 32)

Data suggest that classical onconeural antibodies have no pathological role, and that central nervous system (CNS) damage is mediated by T cells. Nevertheless, these antibodies underlie different tumor associations, disorder-predominant neuropsychiatric features, and response to treatment. (5, 33)

PLE associated with anti-Hu, also called anti-neuronal nuclear antibodies 1 (ANNA-1), occurs in older patients usually with a long history of smoking, as 74% of patients with underlying malignancy have small cell lung carcinoma (SCLC). More frequently than limbic encephalitis (LE), individuals present with sensory neuropathy (54%), cerebellar ataxia (10%), or multisystem disease (11%). More commonly they have depression or hallucinations, but confusion, sleep disturbances, agitation, and anxiety can occur. These symptoms respond poorly to antipsychotics and sedatives, and are followed by the onset of seizures, ataxia, and depressed alertness. (34)

On the contrary, anti-Ma2 is more often seen in younger men, and there is a strong association with testicular cancer. Besides LE, they can also develop diencephalic or brainstem encephalitis, or a disorder with mixed features. Individuals usually display severe short-term memory deficits, gait disturbances, and hypokinesia. Signs of hypothalamic dysfunction (i.e., diurnal hypersomnia, cataplexy, hyperphagia, hormonal deficits, hyperthermia, weight gain, or sexual dysfunction) occur in up to one third of patients. Signs of brainstem dysfunction include cranial neuropathy, nuclear or supranuclear opthalmoparesis, dysarthria, dysphagia, and parkinsonism. Anxiety, OCB, and personality changes are the most frequently reported psychopathological manifestations. Contrarily to anti-Hu, mood disorders and hallucinations are rare. Anti-Ma1 antibodies can also be present and are associated with female gender, older patients, cerebellar dysfunction and malignancies other than testicular, thus predicting poorer prognosis. (35)

Another common antibody in PLE is anti-crossveinless-2/collapsing response mediated protein 5 (anti-CV2/CRMP5). It has a strong association with thymoma and SCLC (in this particular case, it may co-exist with anti-Hu), but can also occur with other malignancies, such as uterine sarcoma. It associates with a wide range of neurological and psychiatric symptoms, being subacute dementia and peripheral neuropathy the most common.

Ocular abnormalities (optic neuritis, posterior uveitis), olfactory or taste loss are more frequent than in other forms of PLE, and the presence of chorea, particularly facial, is highly suggestive. Patients may also display personality changes, depression, confusion,

psychosis, manic mood, OCB, memory deficits, spatial and temporal disorientation. (36-38)

Anti-Ri antibody, also called ANNA-2, is a rare oncoantibody associated with breast, lung, or cervical cancer. It is more frequent in the female gender and has been associated with several neurological paraneoplastic syndromes, most frequently brainstem symptoms, but cerebellar syndrome, peripheral neuropathy, cranial neuropathy, Lambert-Eaton myasthenic syndrome (LEMS), and limbic encephalitis can also coexist. Patients can present with subacute behavioral and neuropsychiatric changes, (39, 40) although gait instability is the commonest symptom at presentation. Most individuals develop multifocal neurological impairment, including ataxia, opsoclonus, myoclonus, jaw-opening dystonia, visual blurring, laryngospasm, sphincter incontinence, cranial nerve impairment, peripheral neuropathy, or myelopathy. Neurological impairment can be severe, and 60% of the patients will require the use of a wheelchair. Contrarily to ANNA-1, gastrointestinal motility disorders are not common. Most patients show concomitant antibodies in serum (Hu, CRMP5, GAD65, but also thyroid peroxidase or thyroglobulin), suggesting predisposition to autoimmunity, and the majority will respond to immunotherapy. (40-42) Other oncoantibodies associated with paraneoplastic neurological syndromes include anti-amphiphysin, anti-Yo/anti-Purkinje cell 1 (PCA-1), and, less commonly, anti-neuronal nuclear antibodies 3 (ANNA-3), anti-Purkinje cell 2 (PCA2), anti-Zic4, and anti-mGluR1, found in several syndromes, especially paraneoplastic cerebellar degeneration or stiff-person syndrome (SPS). (33)

In most patients, PLE will present before cancer is diagnosed, so tumoral screening in the presence of onconeural antibodies is mandatory. Coexistence with anti-surface antibodies, most commonly anti-VGKC, can occur, as does the development of onconeural-antibodies-associated LE without an underlying malignancy, although less frequently. (33, 34)

More recently, anti-Glutamic Acid Decarboxylase (GAD), already associated with diabetes mellitus type 1, SPS, cerebellar ataxia, and epilepsy, has been associated with nonparaneoplastic LE. These patients are more frequently young adults (median age 23 years old), with female predominance. Seizures are universal at presentation and cognitive impairment or psychiatric disturbances are rare. This disorder usually responds to immunotherapy, but to a much less extent than anti-surface disorders, and patients rarely become seizure-free. (43) Another recent study also reported the presence of GAD antibodies in idiopathic limbic encephalitis in children. All had fever and acute clinical deterioration, followed by refractory seizures and a wide spectrum of neuropsychiatric disturbances, even after immunomodulatory therapy. (44)

ANTI-NEURONAL SURFACE AUTOIMMUNE ENCEPHALITIS

Anti-VGKC complex

These antibodies are associated with a wide range of clinical manifestations such as LE, cramp fasciculation syndrome, Isaac's syndrome, LEMS, or Morvan's syndrome.

Previously thought to be a disorder associated with antibodies to the voltage-gated potassium channels (VGKC), recent studies revealed that in fact, the targets are the associated proteins, rather than the channel itself. (45) Most cases are associated with antibodies against leucine-rich glioma inactivated 1 (LGI1) or contactin-associated protein relates 2 (Caspr2), but evidence suggest that other still unrecognized antibodies to VGKC-associated proteins might be involved, explaining such diversity. (46) Although cell-based assays can differentiate them, radioimmunoassay (RIA, still considered the diagnostic gold-standard exam), cannot, and they are still commonly called VGKC-complex antibodies.

Anti-LGI1 is by far the most common and afflicts middle-aged to older patients. It is almost exclusive of patients exhibiting the classic LE clinical presentation triad. Tumor association is infrequent, occurring in 11% of the patients. (45) Concerning Caspr2, the spectrum of associated disturbances is wider (LE, Morvan's syndrome, neuromyotonia,

painful neuropathy) and has a stronger association with cancer, notably thymoma. (47, 48)

Signs of autonomic dysfunction such as sialorrhea and hyperhidrosis are common features. Hyponatremia, often resistant to treatment, (49) and faciobrachial dystonic seizures (FBDS), are other peculiar symptoms. FBDS are almost exclusive of patients with anti-LGI1 antibodies and present as frequent, sudden, brief myoclonic-like movements, with facial grimacing accompanied by ipsilateral arm posturing, often preceding the onset of other symptoms. They are often resistant to antiepileptic drugs but show a good response to immunotherapy. Verbal and visual memory deficits may also be present. (50) Organ specific autoimmunity is seen in one third of these patients, often with a family history of autoimmune disorder. (51, 52)

Common disturbances include behavioral changes, depression, hallucinations and delusions, as well as REM sleep disorders. (52)

Seizures occur in the majority of patients, usually of the temporal lobe type but the frontal lobe can also be involved, without EEG abnormalities even during the seizure, thus can be mistaken for psychogenic non-epileptic seizures. (53)

Anti-NMDAR

This is probably the most common form of autoimmune encephalitis (AE). Since it was first reported in 2006, the number of cases dramatically increased, surpassing the 500 cases, with the California encephalitis project reporting an incidence nearly as high as viral encephalitis. (54)

It is more common in young females (median age 21 years, but age range between 8 months and 85 years), and nearly half are paraneoplastic. Ovarian teratoma is by far the most frequent malignancy, particularly between 12 and 45 years old, especially in females of African or Asian descent. SCLC, neuroblastoma, breast carcinoma, thymoma, testicular cancer, and non-gonadal teratomas may also underlie this disorder, especially in older patients. (55-57)

Unlike most AEs, symptoms are not mainly limited to the limbic system. Clinical manifestations can be subdivided into eight categories: behavior, cognition, memory deficits, seizures, movement disorders, impairment of alertness, autonomic dysfunction, and central hypoventilation. Although initially monosymptomatic, the majority of patients will exhibit symptoms in at least 4 categories within 4 weeks after presentation, with monosymptomatic disease occurring in only 5% of individuals. (56)

The initial clinical presentation differs among age groups: while adults tend to manifest behavioral changes, movement disorders and seizures are more common in children, although psychopathological manifestations can also dominate the clinical picture (29, 58-61), as well as developmental regression. (13) In older adults (> 45 years) predominant symptoms also diverge, as they are more prone to exhibit behavioral changes, and cognitive impairment, and less commonly movement disorders, decreased level of consciousness, or prodromal symptoms. (57) In the extremes of age, no gender preference is observed, with tumors or need for ventilatory support being less frequent. In young adults, this disorder evolves according to a pattern that often starts with a flu-like prodromal phase, characterized by fever, headache, gastrointestinal, or upper respiratory symptoms. Subsequently psychiatric symptoms arise, isolated or along with cognitive decline and/or seizures. Two to three weeks after presentation, movement disorders and autonomic instability surface, followed by impaired consciousness and central respiratory dysfunction, often warranting to admission to the intensive care unit, with the need of ventilatory support. (62)

Psychiatric manifestations include anxiety, agitation, mania, depression, bizarre behavior, delusional and/or paranoid thoughts, and visual or auditory hallucinations, frequently refractory to antipsychotic therapy. In a retrospective study on 100 patients diagnosed with anti-NMDAR encephalitis, all presented psychiatric symptoms, and 77% were first seen by a psychiatrist. (63) Patients are often misdiagnosed with primary psychiatric disorder, usually psychotic illness. Data from 571 patients showed that purely psychiatric

presentation could occur in up to 4%, and in up to 28% in relapsing disease. (62) More commonly these individuals have delusional thinking (74%), half will show aggressive behavior, and hallucinations is noted in 43%. Mood disorders occur in 70%, more often mania. Emotional lability or impulsivity is also common. (64)

Movement disorders include jaw-opening dystonia, facial grimacing, athetosis/dystonia or orolingual-facial dyskinesic movements, opisthotonic postures, and limbs or trunk choreoathetosis. Autonomic dysfunction manifests as tachycardia/bradycardia, hyperhidrosis, persistent pyrexia, central hypoventilation, blood pressure fluctuation, hypersalivation, intestinal pseudoobstruction, and cardiac arrest. (55, 62)

Relapses occur in 24% of patients, with higher incidence in those who did not received immunotherapy(65), and in nonparaneoplastic cases (56), sometimes several years after discharge, (66) justifying long follow-up periods and probably the use of long-term immunosuppression.

Anti-AMPA

Almost all patients are older females (median age 60 years), with relapsing LE. Most cases are paraneoplastic, usually coexisting with breast cancer, lung carcinoma, or thymus cancer. (67) Although only a few cases have been reported, the clinical presentation is variable, since more insidious disease, with progressive memory loss and behavioral changes suggesting dementia has been described, (68) as well as fulminant disease with acute confusion, hypersomnia, visual hallucinations, and combativeness accompanied by severe memory loss and brain atrophy. (69)

Psychopathological manifestations in these patients include confusion, sleep disturbances, aggressiveness, hallucinations, confabulation, lethargy, combativeness and perseveration. Other reported features are seizures, nystagmus, decreased level of consciousness, and gait unsteadiness. (67)

These data are based in a small number of reported patients and further studies are necessary to clarify the clinical presentation, progression and prognosis.

Other anti-neuropil antibodies

Anti-GABA_B AE is an apparently rare and recently described anti-surface LE. Almost all cases are older men (median age 60 years). It is thought to be the most frequent antibody in ALE associated with SCLC previously considered "seronegative". (70) Idiopathic forms have also been reported, more commonly in younger patients (median age 30 years old). Seizures, often unresponsive to treatment, are the predominant symptom at presentation, along with confusion, disorientation, striking memory impairment and behavioral changes, suggesting LE. Psychiatric symptoms reported include psychosis, paranoia, confabulation, delusions, sleep abnormalities, and visual/gustatory hallucinations.

These antibodies can coexist with anti-Hu, SOX-1, TPO, anti-VGKC complex and anti-GAD antibodies, the latter more frequently in paraneoplastic cases. Besides SCLC, neuroendocrine lung cancer and thymus carcinoma can also occur. The outcome is worse as compared to other disorders with anti-neuronal surface antibodies, since response to treatment is frequent, but full recovery is rare and death due to the underlying malignancy is common. (71, 72)

More recently, basal ganglia encephalitis, associated with antibodies against Dopamine receptor 2 (DR2) has been described in children previously diagnosed with encephalitis lethargica, similar to what has been observed with anti-NMDAR AE.(73) In these patients there is a predominance of movement disorders but psychiatric symptoms are also quite common, as do sleep disturbances. None were paraneoplastic, there was no gender or ethnic preference, and in most there was a history of recent infection or immunization. (74)

DIAGNOSTIC APPROACH

Definitive diagnosis of LE will include typical clinical presentation, and either neuroradiological evidence of limbic system involvement, CSF inflammatory changes,

detection of antibodies or response to immunosuppressive therapy. (75) Furthermore, for the disorder to be considered paraneoplastic, other etiologies of limbic dysfunction should be judiciously excluded, and cancer should be demonstrated within 5 years of the diagnosis, in association with a well-characterized paraneoplastic antibody. (33)

However, since some of these new disorders show atypical presentation and normal neuroradiological findings, it has been proposed that the definitive diagnosis of anti-surface mediated CNS disorders could be made by the existence of antibodies in serum or CSF, and clinical improvement under immunotherapy. Furthermore, diagnosis of an autoimmune disorder can be made if patients test positive for anti-surface antibodies, or if there is history of autoimmune disorder or prodromal syndrome, and improvement with immunotherapy. The same authors consider that the diagnosis of authors consider that with antibodies mediated syndrome can be made even in the absence of anti-neuronal antibodies, provided that clinical presentation is compatible and patients present neuronal markers of autoimmunity, or prodromal syndrome, or history of an autoimmune disorder, or response to immunotherapy. (75)

When compared to the viral etiology, seizures, movement disorders, language dysfunction, and psychiatric manifestations are commoner in AE, while autonomic dysfunction is very suggestive of the latter. (54) In the paraneoplastic syndrome associated with anti-CV2/CRMP5, due to the coexistence of chorea and psychiatric symptoms, Huntington's and Wilson's disease should be excluded. Another common presentation can be acute dementia, (76) and other causes of rapidly progressing dementia should also be excluded. Some possible differential diagnoses are listed In Table 3. As previously noted, most of them, particularly the early stage of NMDAR AE, can mimic primary psychiatric disease, most frequently schizophreniform illness with acute disorganized behavior or catatonia. Certain features should raise the suspicion of autoimmune encephalitis, particularly in a first psychotic episode. [Table 4]

Neurological examination is often unremarkable, besides any cognitive or behavioral features. Full blood count, evaluation of renal, hepatic and thyroid function, prolactin, cortisol, serum protein electrophoresis, cobalamin and folic acid level, serum ions, serological screen for autoimmune disorders, toxicological tests (when appropriate) and viral screening tests should be performed.

Afterwards, the standard clinical investigation includes brain MRI, EEG, CSF analysis, autoantibody screening and eventually positron emission tomography (PET). The findings may vary among the different subtypes of AE, as well as their prevalence (table 5). The typical magnetic resonance imaging (MRI) of PLE shows increased temporomesial signal intensity on T2/FLAIR weighted sequences, with swollen anterior structures, unilaterally or bilaterally (asymmetry is common). Later, it evolves to hippocampal atrophy, with persistent swelling remaining after six months mainly in patients with poor response to treatment. (77) Such findings are rarer in anti-neuronal membrane AE. In NMDAR AE normal imaging is the rule, and lesions outside the limbic system are commoner. (78, 79) The same findings can also be seen, although to a lesser degree, in anti-VGKC complex and anti-AMPA AE. (49, 67)

Fluorodeoxyglucose-PET (FDG-PET) often detects changes in the brain when other imaging tests reveal no abnormalities, including MRI. (6, 28, 79-82) There is correlation between the type of antibodies and FDG-PET findings: while classical PLE presents mesiotemporal hypermetabolism, accompanied by hypometabolism in the associative cortices, (80) anti-surface antibodies show more frequently normal scans or findings elsewhere in the brain. Common locations include cerebellum, thalamus, parietal or occipital cortices. (79) In NMDAR, findings have been further divided into two major patterns. The first one is more often seen in younger patients, and consists of increased metabolism in the temporal and orbitofrontal cortex, with hypometabolism in the occipital cortex and diffuse borderline hypermetabolism in the cerebellum, usually referred to as fronto-temporo-occipital gradient. (83) The second pattern is seen in older patients, with less striking symptoms and without seizures. In this group, FDG-PET shows diffuse decreased metabolism, more striking in the temporal lobes, with normal uptake in

subcortical structures.(84) It is still not clear whether these findings represent different stages of disease evolution.

EEG abnormalities are almost universal, usually nonspecific, including diffuse or focal slowing, rhythmic intermittent frontal or temporal delta activity (FIRDA or TIRDA), or temporal epileptiform activity. (85, 86) In anti-NMDAR AE, a specific pattern, called “extreme delta brush” (EDB) has been observed in 30% of patients in small series. This pattern has not been described in any other disorder, and these patients show more frequently a normal MRI, longer hospitalization, and worse prognosis, suggesting that it might be a marker of more severe disease. (84, 87) In the pediatric group, EEG findings also seem to have prognostic value: while patients with normal physiological background activity (PBA), with unilateral or focal abnormalities, presented with milder neurological impairment and better outcome, those patients who had more diffuse abnormalities without PBA showed more severe neurological symptoms and a poorer outcome. (88) CSF analysis often reveals lymphocytic pleocytosis, increased protein concentration or presence of oligoclonal bands (OCB). (32) OCB are a highly specific finding of AE (96%), particularly of NMDAR or GAD AE, but sensitivity is low (36%). (89) In anti-NMDAR AE, over 80% of patients have an abnormal CSF at presentation; progression of findings is usually characterized by an early phase with lymphocytic pleocytosis, with or without elevated protein levels, followed by the decrease of white blood cells in CSF and the appearance of OCB. On the other hand, with anti-VGKC only half of the individuals show abnormal CSF screen and even rarely present OCB. (90, 91)

Antibody titers can be determined in both serum and CSF. Gold-standard test differs among the different antibodies, since onconeural antigens are linear, and can be detected either by immunoblotting, ELISA or immunohistochemistry using mammalian brain; anti-surface antibodies are directed against conformational epitopes, losing their reactivity when the antigen is denatured. So, they require either an adapted immunohistochemistry protocol, the use of live neurons, or cell-based assays. (92)

Contrarily to anti-nuclear antibodies, in anti-neuropil-associated AE, antibody titers often correlate with symptomatic improvement (4, 93), but they can also decrease with time, even without therapy and irrespectively of clinical outcome (90, 94), their levels fluctuate due to immunosuppressants (particularly in serum), and they can remain elevated for years after recovery. (66, 92, 95)

Finally, further investigation to exclude an underlying neoplasm should be considered in all cases, since the neurological presentation often precedes the diagnosis of cancer. Tumor screening should be focused on most commonly associated malignancies. In children at least an ultrasound and MRI of the abdomen is advised. (60) Other advised screening tests are listed on table 6. Imaging screening might not be sensible enough to detect microtumors, thus repeated exams every 3 to 6 months during 4 years is recommended if no malignancy is found in the meantime. (96) In case of relapsing disease, the possibility of an undetected or recurrent tumor should be considered.

MANAGEMENT AND FOLLOW-UP

Once other relevant causes have been ruled out, immunotherapy should be considered in all cases. Since most disorders are rare and/or were recently classified, there are no robust randomized clinical trials able to provide evidence-based recommendations..

Current treatment options are based on case reports and uncontrolled case series.

Cancer treatment should always be carried out, when applicable, (56, 62) since combined treatment typically results in more favorable outcome than immunotherapy alone. (97)

Treatment includes high-dose corticosteroids (CT), intravenous immunoglobulin (iv-Ig) and plasma exchange as first line immunotherapy. Rituximab, azathioprine and cyclophosphamide are considered second line therapeutic interventions, thus prescribed when individuals fail to respond to first line drugs. Due to the high occurrence of relapsing disease, chronic immunosuppressant therapy with mycophenolate mofetil or azathioprine can also be considered.

It has been suggested that the response to treatment could be evaluated with the modified Rankin Scale (mRS); treatment has been considered successful if the score lowers at least one point on mRS. (56)

Classic anti-nuclear PLE usually follows a monophasic course, even with combined treatment, and prognosis is poor, with extremely rare cases of spontaneous recovery without treatment. (98) The exception to this rule is anti-Ma2, usually with better prognosis, with one third of patients having a complete recovery, and clinical stabilization in one fifth. Some features associate with better outcome, including male gender, younger age (< 45 years), with complete response to treatment with underlying testicular tumor, absence of anti-Ma1 antibodies, and limited involvement of the CNS. (35) These severity hallmarks differ for anti-Hu, with older patients (> 60 years), RMS > 3, involvement of more than one area of the CNS, and absence or delayed treatment being considered mortality predictors. (31, 34)

In anti-VGKC-complex AE, immunotherapy has been tried with intravenous methylprednisolone 1 gram or 30-50 mg/kg for 5 days, or iv-Ig 0.4 g/kg for 3-5 days, or 5 to 7 cycles of plasmapheresis (on alternate days). If patients respond to this treatment within 6 weeks, then a corticosparring agent can be initiated. If not, or in case of relapsing disease, second line therapy should be promptly considered. (51) In these patients, good outcome is correlated with early treatment, and the initial therapy regiment (with CT and iv-Ig apparently better than CT alone). (91) In cases of presentation with FBDS, immunotherapy should also be administered, since many patients are resistant to antiepileptic drugs (AED). Furthermore, evidence suggests than immunotherapy at this early stage might prevent the emergence of cognitive impairment. (91, 99)

In anti-NMDAR AE, the most commonly used strategy is iv-Ig 0.4 g/kg/day for 5 days, plus methylprednisolone 1 g/day for 5 days; plasma exchange is postponed for treatment failure cases. (100) If no improvement occurs after 4 weeks of first therapy, second line drugs should be considered. (56) Once again, early treatment, younger age, no need for intensive care, and longer follow up are associated with better prognosis.(56, 94)

Electroconvulsive therapy (ECT) has been used to treat these patients, with rapid improvement of autonomic dysfunction, psychosis, delusions, stupor and catatonia, and it might be used as a second line treatment in patients refractory to pharmacological therapy. (101) Nevertheless, it is still a controversial procedure, with a wide range of reported clinical response. (102)

Figure 1 summarizes how clinical features can guide antibody screening in cases of suspected AE.

CONCLUSION

It is a fact that autoimmune encephalopathies, particularly those with antibodies directed against the cell surface membrane and associated proteins, can present with psychiatric symptoms, and many of these individuals seek psychiatric help first. Hence the importance of including this disorder in the list of possible differential diagnoses in patients presenting with a new-onset or atypical psychotic or mood disturbance, especially if there is no history of mental illness, not only in elderly patients but also in young adults and children. (103)

After exclusion of commoner causes, antibody testing should be performed, since no clinical symptom or finding is pathognomonic, but some are highly suggestive of a given disorder (figure 1). Antibody screening may provide the correct diagnosis, can help direct cancer screening, thus avoiding unnecessary costs, and also provides clues regarding prognosis and likely response to therapy.

Some patients may show negative antibody screening on the currently available tests, even when clinical presentation is archetypal. (104-107) These patients may also improve with immunosuppressant therapy, thus immunotherapy is strongly advised in cases with highly suggestive clinical presentation, after viral etiology has been appropriately excluded; tumor screening should also be carried out. (108) Although complete recovery in the absence of immunotherapy has been reported, prompt prescription is associated

with a better prognosis in most instances. Patients who do not receive proper treatment usually suffer from slower recovery, longer hospitalization periods, and a higher risk of relapsing disease. (65)

The startling number of cases of autoimmune encephalitis described in the last decade suggests that this is not a rare disorder and it is likely underdiagnosed, thus clinicians should keep a low suspicion index. As autoimmune encephalopathies become more widely recognized, additional autoantibodies, features and atypical presentations are likely to be identified, as well as their real prevalence. The prevalence of autoimmunity in psychiatric disorders such as schizophrenia is the object of current research (103, 109), but its true contribution is yet to be accessed, and a role for immunotherapy is yet to be determined in these conditions. Also, further exploration is needed in order to accurately assess the epidemiology of autoimmune encephalitis, the clinical course of its various subgroups, and also to determine the most effective management strategies during acute illness and after discharge.

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Antibody	Patient Features	Associated malignancies	Common psychiatric symptoms	Other findings
Hu	Older patients Smoking history	SCLC	Depression Hallucinatory activity Sleep disturbances Anxiety disorders	Seizures Ataxia Consciousness impairment Painful sensitive neuropathy Gastrointestinal motility disorders
Ma2	Young males Older women	Testicular germ cell tumor SCLC	Sleep disturbances Anxiety disorders OCB Mood disturbances	Supranuclear gaze palsy Cranial neuropathy Parkinsonism Hypothalamic dysfunction
CV2/ CRMP5		SCLC Thymoma Uterine sarcoma	OCB Personality changes Mood disturbances Psychosis Subacute dementia	Chorea Ocular disturbances (uveitis, optic neuritis) Olfactory/ taste loss Cerebellar ataxia Peripheral neuropathy Hu-AB can coexist
Ri	Older women Smoking history	Lung cancer Breast cancer Cervical cancer Bladder cancer	Behavioral changes	Ataxia Opsoclonus-myoclonus Laryngospasm Jaw-opening dystonia Visual blurring

TABLE 1- Clinical features of the different oncoantibody associated disorders.
Abbreviations: AB: Antibodies; CV2/CRMP5: Crossveinless-2/collapsing response mediated protein 5; OCB: Obsessive-compulsive behavior; SCLC: Small cell lung cancer.

Antibody	Patient Features	Associated malignancies	Common psychiatric symptoms	Other findings
LG11	Middle age to older patients males Personal/familiar history of autoimmune disorders ^a	Rare	Behavioral changes Depression Delusions Hallucinations REM sleep disorders	Hyponatremia FBDS Seizures Autonomic instability Neuromyotonia Ataxia Intestinal pseudo-obstruction
Caspr2	Older males Personal/familiar history of autoimmune disorders ^a	Thymoma SCLC	Severe insomnia Hallucination Personality changes Delusion	Autonomic dysfunction Weight loss Neuromyotonia Painful neuropathy Seizures
NMDAR	Younger patients and children Paraneoplastic cases more common in non-caucasian females	Ovarian teratoma SCLC Neuroblastoma Breast carcinoma Thymoma	Delusion and hallucination Anxiety disorders Aggression and agitation Bizarre behavior Mood disorders	Prodromal flu-like Dissociative anesthesia Decreased conscience Seizures Autonomic instability Orofacial dyskinesia, facial grimacing, jaw opening dystonia Opisthotonus, catatonic postures
AMPA	Older females	Breast cancer Lung carcinoma Thymoma	Behavioral changes Sleep disorders Confabulation Hallucination	Short-term memory impairment Seizures Confusion Relapsing disease
GABA _B	Older men Younger nonparaneoplastic group	SCLC Thymoma	Psychosis Hallucination Sleep disturbances Paranoia	Short-term memory impairment Seizures at presentation

TABLE 2- Clinical features of the most common anti-surface autoimmune encephalitis. Abbreviations: AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2: contactin-associated protein relates 2; FBDS: Fachiobraquial dystonic seizures; GABA_BR: Gamma-aminobutyric acid receptor; LG1: Leucine-rich glioma inactivated 1; NMDAR: N-methyl-D-aspartate receptor; SCLC: Small cell lung cancer; VGKC: Voltage-gated potassium channel. ^a Data relates to anti-VGKC-complex-associated encephalitis.

Paraneoplastic encephalitis	Endocrine dysfunction (Hypothyroidism)
Non-paraneoplastic autoimmune encephalitis	Toxic-metabolic encephalopathy (e.g. sepsis, liver failure)
Viral encephalitis	Vitamin deficiency (Wernicke-Korsakoff encephalopathy, B12 or folic acid deficiency)
Dementia, including neurodegenerative diseases (e.g. Alzheimer disease, Frontotemporal dementia)	Autoimmune systemic disorder (Lupus erythematosus, Vasculitis, Sjögren's syndrome)
Malignancy (glioma, lymphoma)	Neurosyphilis
Temporal lobe seizures	Creutzfeldt-Jakob disease
Wilson's Disease	Primary psychiatric disorder
Huntington's disease	

TABLE 3 - Differential diagnosis of suspected autoimmune encephalopathies.

Recent flu-like syndrome No past psychiatric illness Rapid onset of psychosis and/or catatonia Seizures/neurological dysfunction Known history of malignancy, especially if SCLC, teratoma or thymus cancer Signs of autonomic dysfunction Worsening of symptoms after antipsychotic ministration Refractory hyponatremia Long history of smoking Personal/family history of auto-immune disease

TABLE 4 - features that should raise the suspicion of autoimmune etiology in case of atypical psychiatric presentation, particularly in first episode psychosis or mania.
Abbreviation: ECT: electroconvulsive therapy; SCLC: Small cell lung cancer.

Antibody	EEG changes	MRI	CSF abnormalities	Prognosis
Onco-AB	Common, non specific	Temporomesial hyperintensities Ma2: lesions outside the limbic system are common	Common lymphocytic pleocytosis Mild elevation of protein levels	Hu: Poor, median survival 12 months Ma2: 50-70% clinical stabilization/ improvement CV2/ CRMP5: poor, median survival 48 months; 18 months if anti-HU antibodies coexist Ri: good response to treatment; better than CV2 or Hu
LG11	Common, non specific	Temporomesial hyperintensities Cortical atrophy Mesiotemporal and basal ganglia hypermetabolism	Rare Slight increase in proteins level Seldom OCB	Excellent response to immunotherapy Improvement: 80% Full recovery: 24% Mortality: 6%
Caspr2	Common, non specific	Same as LG11	Same as LG11	Poor prognosis, although good response to therapy
NMDAR	Common, non specific "Extreme delta brush" pattern	Rare Abnormalities outside the medial temporal lobe Fronto-temporo-parietal gradient on PET	Very common Mild pleocytosis Raised protein level Oligoclonal bands	Good Full recovery: 70-80% Mortality: 10%
AMPA	Common, non specific	Temporomesial hyperintensities Lesions outside the limbic system (i.e., anterior septal nuclei, cerebellum)	Common Lymphocytic pleocytosis	Poor, although good response to therapy Relapses are common
GABA _B R	Common, non specific	Common Lymphocytic pleocytosis	Abnormal in half of the cases	Poor Full recovery: 18% Partial response: 36%

Table 5 - Correlation between associated antibody frequency of findings in auxiliary exams and prognosis. Abbreviations: AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; Caspr2: contactin-associated protein relates 2; CV2/CRMP5: crossveinless-2/collapsing response mediated protein 5; GABA_BR: Gamma-aminobutyric acid receptor; LG1: Leucine-rich glioma inactivated 1; NMDAR: N-methyl-D-aspartate receptor; PET: positron emission tomography; OCB: oligoclonal bands; VGKC: voltage-gated potassium channel

Suspected malignancy	Auxiliary exams
SCLC	Chest CT; if negative FDG-PET
Non-SCLC	Chest CT; if negative FDG-PET
Thymoma	Chest CT
Testicular cancer	Ultrasonography; if negative pelvic CT
Teratoma	Pelvic ultrasonography; if negative CT/MRI of pelvis/abdomen; if negative chest CT
Breast cancer	Mammography; if negative MRI; if negative FDG-PET

TABLE 6 - Recommended auxiliary exams according suspected underlying malignancy. Abbreviations: CT: computed tomography; FDG-PET: fluorodeoxyglucose positron emission tomography; MRI: magnetic resonance imaging; SCLC: small cell lung cancer

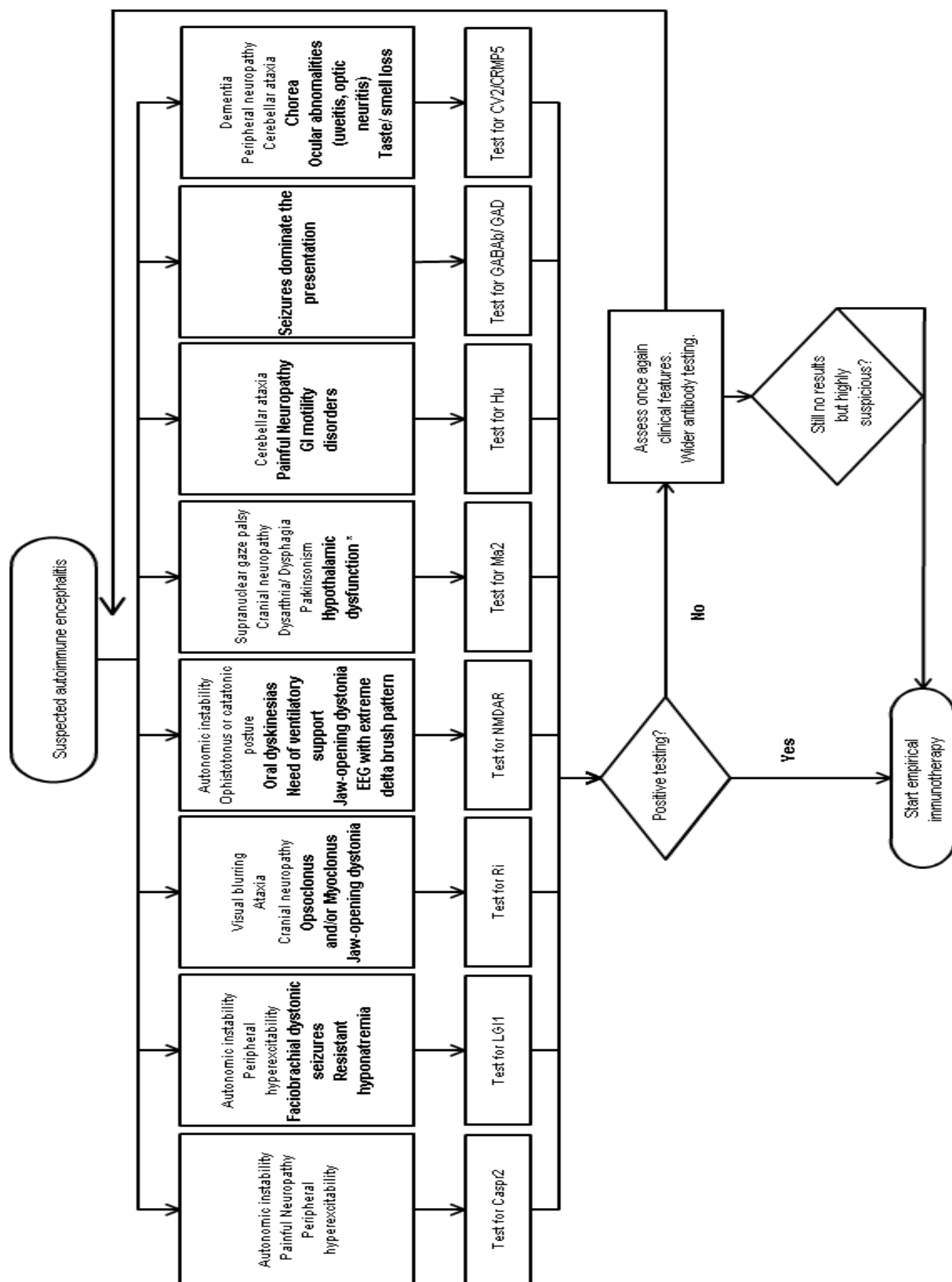


Figure 1 - Algorithm for antibody testing in autoimmune encephalopathies. Abbreviations: AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor CV2/CRMP5: crossveinless-2/collapsing response mediated protein 5; GABABR: GABA_B -aminobutyric acid receptor; GAD: Glutamic Acid Decarboxylase; NMDAR: N-methyl-D-aspartate receptor; VGKC: Voltage-gated potassium channel. * Hypothalamic dysfunction includes diurnal hypersomnia, cataplexy, hyperphagia, hormonal deficits, hyperthermia, weight gain, and sexual dysfunction

AGRADECIMENTOS

Devo um especial agradecimento ao Dr. João Massano pela orientação durante todo o processo que culminou com a elaboração deste projeto. Agradeço a disponibilidade, a amabilidade, a paciência, os conselhos e o conhecimento transmitido, sem os quais a abordagem de um tema já de si desafiante ter-se-ia tornado num trabalho muito mais complicado.

Queria também agradecer ao Professor Rui Coelho pela disponibilidade e pelo aconselhamento.

A todos os meus colegas de curso, que tornaram este percurso uma aventura única, dentro e fora das portas da faculdade, cujo peso que tiveram nestes seis anos não consigo sequer quantificar.

A todos os docentes, médicos e não-médicos, que me ajudaram a construir as bases do conhecimento médico, e que me ajudaram na minha evolução profissional e pessoal.

Por último, um especial agradecimento à minha família, pelo apoio incondicional e pela paciência que sempre demonstraram, sem os quais este projeto, a finalização deste mestrado ou a minha formação como pessoa e futura médica nunca teriam sido possíveis.

ANEXOS

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1. Aims and Scope

The International Journal of Clinical Neurosciences and Mental Health is an open-access peer-reviewed journal published trimonthly by ARC Publishing.

Our goal is to provide high-quality publications in the areas of Psychiatry and Mental Health, Neurology, Neurosurgery and Medical Psychology. Expert leaders in these medical areas constitute the international editorial board.

The journal publishes original research articles, review articles, drug reviews, case reports, case snippets, viewpoints, letters to the editor, editorials and guest editorials.

The International Journal of Clinical Neurosciences and Mental Health follows the highest scientific standards, such as the CONSORT / STROBE guidelines and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (ICJME).

The journal offers:

- Trusted peer review process
- Fast submission-to-publication time
- Open-access publication without author fees
- Multidisciplinary audience and global exposure

2. Types of papers

The International Journal of Clinical Neuroscience and Mental Health publishes scientific articles in the following categories:

- Original research articles.
- Reviews.
- Drug reviews.
- Case reports.
- Case snippets.
- Viewpoints.
- Letters to the editor.
- Editorials and guest editorials.

2.1. Original research articles

The International Journal of Clinical Neurosciences and Mental Health welcomes original clinical research related with psychiatry, mental health, medical psychology, neurosurgery and neurology.

Reports of randomized clinical trials should follow the [CONSORT Guidelines](#) and reports of observational studies should comply with [STROBE Guidelines](#).

Body text of an Original Research Article should have no more than 4000 words (word count excludes title page, abstract, acknowledgments, references and tables). A maximum of 6 illustrations (figures or tables) are allowed. Supplementary online material may be submitted at the editor discretion.

2.2. Review articles and Drug Reviews

Review articles on CNS-related drugs, psychiatry, mental health, medical psychology, neurosurgery and neurology topics are welcome. Both invited and unsolicited submissions are accepted.

Manuscripts should be limited to a maximum of 4,500 words, excluding title page, abstract, acknowledgments, references and tables.

2.3. Case reports and case snippets

Case Reports and Case Snippets should have no more than 750 and 500 words, respectively (word count excludes references); one figure or table can be included.

Only highly meaningful Case Reports are accepted, including major educational content or major clinical findings. Case Snippets should describe a diagnosis or therapeutic challenge.

2.4. Viewpoints

Viewpoints should provide an expert opinion on important topics for medical research or practice, with possibility for covering social and policy aspects. This section encourages dialogue and debate on relevant issues with expert views based on evidence.

Viewpoints are limited to 1500 words (word count excludes references) and can include one figure or table.

2.5. Letters to the Editor

Letters to the Editor should share views on published articles, any findings insufficient for a research article or present ideas of any subject in the scope of the journal.

Letters to the Editor have a maximum of 600 words (including references) and can include one figure or table.

2.6. Editorials and Guest Editorials

Authors are invited by the Editor-in-Chief to comment on specific topics and express their opinions. Editorials and Guest Editorials have a maximum of 1,000 words and can include one figure or table.

3. Manuscript Submission

These instructions advise on how the manuscript should be prepared and submitted. Manuscripts that do not comply with the guidelines will not be considered for review.

All manuscripts should be prepared in A4-size or US-letter size, in UK or US English.

Manuscripts should be submitted in *.doc and *.pdf formats, in the appropriate section of the journal website: [IJCNMH online submission](#).

3.1. Cover Letter

A cover letter should be submitted together with the manuscript, in *.doc or *.pdf format, addressed to the Editor-in-Chief.

A template for the cover letter is available for [download](#).

The cover letter should contain statements about originality of your publication, Ethics Committee approval and informed consent (if applicable), conflicts of interest and why in your opinion your manuscript should be published.

3.2. Manuscript Preparation

The manuscript must be divided in 2 files: the Title page (submitted in *.doc format and *.pdf formats) and the Manuscript body (submitted in *.doc and *.pdf formats).

Title page

This should be submitted as a separate file from your manuscript (to assure anonymity in the peer review process) and should include:

- Article title.
- Authors' names, titles (e.g. MD, PhD, MSc, etc.) and institutional affiliations.
- Corresponding author: name, mailing address, telephone and fax numbers.
- Keywords (maximum of 10).
- A running head (up to 50 characters).
- Abstract word count (up to 250 words).
- Body text word count.
- The number of figures and tables.

Manuscript body:

The Manuscript body must be anonymous, not containing the names or affiliations of the authors. Manuscript body must be structured in the following order: title, abstract, body text, acknowledgements, references, tables, and figures captions/legends.

- The text must be formatted as follow:
- Arial fonts, size: 11 points.
- Single line spacing (see paragraph menu).
- Aligned to the left (not justified).

Showing continuous line numbers on the left border of the page. For MS Word you can add line numbers by going to: Page Layout -> Line Numbers -> select "Continuous"; for OpenOffice: Tools -> Line Numbering -> tick "Show numbering".

Title

A descriptive and scientifically accurate article title should be provided.

Abstract (250 words maximum)

An abstract should be prepared for Original Research Articles, Review Articles and Drug Reviews.

Should be structured and include: background/objective, material and methods, results, and conclusions. These sections should be separated by the respective headings.

If the publication is associated with a registered clinical trial, the trial registration number should be referred at the end of the abstract.

Body text**Original research articles**

Original research articles should be structured as follows:

Introduction: Should present the background for the investigation and justify its relevancy. Claims should be supported by appropriate references. Introduction should end by stating the objectives of the study.

Methods: Should allow the reproduction of results and therefore must provide enough detail. Appropriate subheadings can be included, if needed.

Results: Should include detailed descriptions of generated data. This section can be separated into subsections with concise self-explanatory subheadings.

Discussion and Conclusions: Should be brief but comprehensive and well argued, summarise and discuss the main findings, their clinical relevance, the strengths and limitations of the study, future perspectives with suggestion of experiments to be addressed in the future.

Review articles and Drug Reviews

These types of articles should be organized in sections and subsections.

Acknowledgements

This section should name everyone who has contributed to the work but does not qualify as an author. People mentioned in this section must be informed and only upon consent should their names be included along with their contributions. Financial support (with grant number, if applicable) should also be stated here.

Any conflict of interests should be declared. If authors have no declaration it should be written: "The authors declare no conflict of interests".

References

References citation in the text should be numbered sequentially along the text, within brackets.

The use of a reference management tool (such as Endnote or Reference Manager) is recommended. References must be formatted in Vancouver style.

Only published or accepted for publication material can be referenced. Personal communications can be included in the text but not in the references list.

Tables

Tables should be smaller than a page, without picture elements or text boxes. Tables should have a concise but descriptive title and should be numbered in Arabic numerals. Table footnotes should explain any abbreviations or symbols that should be indicated by superscript lower-case letters on the body table.

Figures

Figures should have a concise but descriptive title and should be numbered in Arabic numerals. If the article is accepted for publication, the authors may be asked to submit higher resolution figures. Copyright pictures shall not be published unless you submit a written consent from the copyright holder to allow publishing.

Each figure file shall not be larger than 30MB.

Figures should be tested and printed on a personal printer prior submission. The printed image, resized to the intended dimensions, is almost a replication of how the picture will look online. It shall be clearly perceived, non-pixelated nor grainy. Only flattened versions of layered images are allowed. Each figure can only have a 2-point white space border, thus cropping is strongly advised. For text within figures, Arial fonts between 8 to 11 points should be used and must be readable. When symbols are used, the font information should be embedded.

Photographs should be submitted as *.tif or *.eps at high-resolution (300 dpi or more). Graphics should be submitted in *.eps format. MS Office graphics are also acceptable.

All figures, tables and graphics should have white background and not transparent.

Lines, rules and strokes should be between 0.5-1.5 points for reproducibility purposes.

3.3. Supporting Information

Code of Experimental Practice and Ethics

The minimal ethics requirements are those recommended by the Code of Ethics of the World Medical Association (Declaration of Helsinki). Authors should provide information regarding ethics on research participants, patient informed consent, data privacy as well as competing interests. If the authors have submitted a related manuscript elsewhere should disclose this information prior submission.

Nomenclature

All units should be in International System (SI). Drugs should be designated by their International Non-Proprietary Name (INN).

3.4. Submission Checklist

Please ensure you have addressed the following issues prior submission:

- Details for competing interests.
- Details for financial disclosure.
- Details for authors contribution.
- Participants informed consent statement.
- Contributor copyright authorization of figures included in the manuscript, not produced by the authors and subjected to copyright.
- Authorship, affiliations and email addresses are correct.

- Cover letter addressed to the Editor-in-Chief.
- Identification of potential reviewers and their email addresses (to be introduced at the online submission platform).
- Manuscript, figure and tables comply with the author guidelines, including the correct format, SI units and standard nomenclature.
- Separated files for Title page (*.doc and *.pdf) and Manuscript body (*.doc and *.pdf)—4 in total.
- Manuscript body does not contain the names or affiliations of the authors.

If you have any questions, please contact ijcnmh@arc-publishing.org

4. Overview of the Editorial Process

The International Journal of Clinical Neurosciences and Mental Health aims to provide an efficient and constructive view of the manuscripts submitted to achieve a high quality level of publications. The editorial board is constituted by expert leaders in several areas of medicine particularly in Clinical Neuroscience and Mental Health.

Once submitted, the manuscript is assigned to an editor which evaluates and decides whether the manuscript is accepted for peer-review. At this initial phase, the editor evaluates if the manuscript fulfils the scope of the journal according to the content and minimum quality standards. For peer-review, one or two additional expert field editors will comment on the manuscript and decide on whether it is accepted for publishing with minor corrections or not accepted for publishing. The editor may ask authors to resubmit after major revision. Decision is based on technical and scientific merits of the work. Reviewers can be asked to be disclosed or stay anonymous. Authors can exclude specific editors or reviewers from the process, upon submission, a rationale should be provided.

Upon evaluation, an email is sent to the corresponding author with the decision. If accepted, the manuscript enters the production process. It takes approximately 6-7 weeks for the manuscript to be published.

4.1. Appeal Process

The editors will respond to appeals from authors which manuscripts were rejected. Their interests should be sent to the Editor.

Two directions can be followed:

- If the Editor does not accept the appeal, further right to appeal is denied.
- If the Editor accepts the appeal, a further review will be asked. After the new review, the editor can reject or accept the appeal. If rejected, nothing else can be done, if accepted the author is able to resubmit the manuscript.

The reasons for not accepting a manuscript for consideration can be:

- The manuscript does not follow the scope of the journal.
- The manuscript has potential interest but there are methodological concerns after peer-review or editorial examination.